REMARKS

This is in response to the Office Action of November 2, 2007. Applicants gratefully acknowledge the Examiner's indication that claims 14 and 15 herein are allowable in substance. Claim 12 is amended to recite the "A" and "B" type solvents formerly recited in claim 13. Claim 13 is accordingly amended to recite preferred "A" and "B" type solvents, and new claims 16-18 are added to recite specific disclosed "A" and "B" type solvents. No new subject matter is introduced by this Amendment. Claims 12-16 are pending in the application.

Rejection under 35 U.S.C. § 112

Claims 12 and 13 were rejected under the first paragraph of 35 U.S.C. § 112 as failing to comply with the written description requirement. Office Action, page 2. Claims 12 and 13 were rejected under the second paragraph of 35 U.S.C. § 112 as failing to define the invention properly. Office Action, pages 2-3. Applicants respectfully submit that claims 12 and 13 as amended herein satisfy all requirements of the first and second paragraphs of 35 U.S.C. § 112.

Rejection under 35 U.S.C. § 103

Claims 12 and 13 were rejected 35 U.S.C. § 103(a) as being unpatentable over WO 03/051362 A2 (Lifshitz-Liron). Office Action, pages 3-6. The rejection is respectfully traversed.

The Examiner contends that the reference teaches "a similar process wherein type A solvent is acetone and type B is diethyl ether. The product is left to precipitate without seeding." Office Action, page 4. The Examiner concludes that at least one embodiment of the presently claimed process is merely an obvious variation of that process. Applicants respectfully disagree with the Examiner's findings.

Examples 22-25 of the reference describe generally similar processes using alcohols as type A solvents and an ether solvent as a type B solvent. Although the product is described as polymorph form I, the crystallographic purities of the products of Examples 22-25 are not disclosed.

This fact is very important, because according to Example 17 of the reference, the use of a similar process leads to an amorphous product. According to Example 21 a mixture of the polymorph form 1 and the amorphous form is produced. According to Example 12, in which acetonitrile was used as an A type solvent, the thermodynamically most stable polymorph form II is produced.

In the pharmaceutical industry the polymorph purity is of great significance, for at least three reasons: (1) The different polymorph and amorphous forms have dissolution rates differing from those of the pharmaceutical compositions. (2) Furthermore, other physical properties, e.g. gliding, can influence the quality and the preparation process of the pharmaceutical composition. (3) The presence of the less stable amorphous form, even as a contaminant, can cause recrystallization of the active ingredient to a stable crystalline form, e.g. to the most stable polymorph form 2, during storage before or after preparation. As a result of this, the pharmaceutical effect of the product can be altered.

A further drawback of the process suggested by Lifshitz-Liron is that his clopidogrel concentrations are very low. The volumes of solvents used in the reference are about 350 times the weight of the clopidogrel hydrogensulphate obtained. In contrast, in the only dissolution-precipitation Example in which lower solvent excess is used (Example 41), polymorph V is formed. The Lifshitz-Liron processes cannot be used to produce polymorph form 1 in higher concentration. They are accordingly unacceptable from an industrial point of view.

Alleged obvious modifications

The Examiner contends that using a type B solvent to add sulphuric acid is an obvious modification available to the preference of an artisan. Therefore, the instant invention is contended to be *prima facie* obvious from the teachings of Lifshitz-Liron. One of ordinary skill in the art would have allegedly known to seed the reaction mixture at the time the invention was made.

Applicants respectfully disagree with this opinion stated by the Examiner. The use of only one or two of these technical features discourages the person of ordinary skill in the art from using them, or further combinations thereof, as explained below.

Reaction of clopidogrel base with sulphuric acid in a type A solvent in situ: As admitted by the Examiner, there is no example among the precipitation examples of Lifshitz-Liron in which the *in*

situ reaction of clopidogrel and sulphuric acid is directly followed with a precipitation process using an "antisolvent." In cases when the *in situ* reaction of clopidogrel base and sulphuric acid is used, the reaction mixture is boiled for hours before filtration of the cooled product. During the reaction and crystallization processes, most of the parameters are changed, such as the local concentrations of the compounds and the product, the local changes of the temperature of the mixture depending on the reaction heat and the mixing, and so on.

According to Chapter 11 of the Crystallization Technology Handbook (pages 513-514), precipitation in cases of reaction crystallization is very problematic. The form of the resulting product cannot be predicted – it can be either in a crystalline or an amorphous form.

> Precipitation differs from these classical processes in that the supersaturation, which is required for the crystallization, no longer results from an action on the physical properties or the solution. It is obtained by a chemical reaction between two soluble components leading to a less soluble product which crystallizes. The reactants can be molecules or ions. The reaction crystallization may proceed via a third intermediate, a dissolved molecule, which becomes solid afterwards. Alternatively, the reactants can directly lead to a very sparingly soluble precipitate. The generated solids can be crystalline or amorphous. Reticulation of the suspended, solid particles may take place, and the suspension is then called a gel.
>
> In both cases, the reaction and the crystallization occur simultaneously and have their own kinetics. Both have to be taken into account. Thus, it will be necessary to consider the crystallizer as a chemical reactor with complex kinetics and to apply the chemical engineering methodology for its design and characterization. ...
>
> Hence, the study of reaction crystallization is more difficult than that of classical crystallization, because the crystal generation depends on several processes, which all have their own kinetics (e.g., chemical reaction, crystallization, and mixing). The competition between these three steps generally results in (a) rapid crystallization and especially nucleation, which is problematic to keep under control, and (b) multiple zones in the apparatus showing different mixing conditions and, consequently, very different crystallization and reaction conditions.

Therefore, a person of ordinary skill in the art would avoid this process type for the preparation of a particular polymorph form of an active ingredient.

These facts are supported by the present application as follows: In Comparative Example B of the present invention, the reaction of clopidogrel base and sulphuric acid is carried out in dichloromethane (without seeding), then the mixture is added to an ether type solvent. The

result is, as expected, an amorphous product. Three similar experimental results are given in Table 2 of the present application. Such results would discourage the person of ordinary skill in the art from using a reaction crystallization method.

Seeding: The Examiner contends that the seeding feature is an obvious feature of the present invention in light of Lifshitz-Liron, in which seeding is suggested for acceleration of the crystallization. Applicants disagree. In the present invention, the role of the seeding crystals is not only to accelerate the crystallization, but also to help to obtain the required crystal form, namely polymorph form 1. Lifshitz-Liron mentions the possibility of a seeding process, but only as a general option.

For example, a common seeding process for the preparation of clopidogrel hydrogensulphate is shown in the description of WO 99/659145[1]. In light of the knowledge of persons of ordinary skill in the art evinced by WO 99/659145, the present invention is not seen to involve a conventional seeding process. Examples 2 and 3 of that application show a conventional seeding process, namely clopidogrel polymorph form 2 is being prepared using seeding crystals. The amount of seeding crystals was conventional, 0.032-0.081 mole % based on one mole crystallized clopidogrel polymorph form 2. The adoption of the usual seeding process to these dissolution-precipitation processes using seeding crystals of polymorph form 1 of clopidogrel hydrogensulphate results in the undesired polymorph form 2 according to Comparative Example "B" of the present invention. Even using 1.57 weight % of clopidogrel hydrogensulphate polymorph 1 for seeding, clopidogrel polymorph form 2 is formed. This means that even the use of 20-50 times more seeding crystals, based on Examples 2 and 3 of WO 99/659145, is an unsuitable method to get the appropriate polymorph form.

As demonstrated, therefore, the combination of a normal seeding process and *in situ* salt formation does not alone lead to the formation of the required crystalline form during a reaction crystallization process.

Using type B solvent (change of the polarity of the solvent during or immediately after the reaction of clopidogrel base and sulphuric acid): Applicants respectfully disagree with the opinion of the Examiner in which he states that using type B solvent to add sulfuric acid is an

[1] Listed in an IDS form attached to the outstanding Office Action.

obvious modification. On the one hand, during a reaction crystallization process, the circumstances are very unfavorable as mentioned above. It is difficult to control these processes because of the changes of local circumstances, e.g., concentrations of the reagents and products. The person of ordinary skill in the art would not increase the uncertainty of the process with the intensive change of the polarity of the reaction mixture during the reaction or immediately after the reaction. On the other hand, the required result cannot be achieved without this change. It is clear in light of the description of the present invention that the presence of only one type of solvent does not result in an appropriate product. See, for instance, Comparative Example "A" using acetone as single solvent.

The last three paragraphs on page 8 and Table 1 on page 9 of Applicants' specification show that using either one solvent (e.g. acetone, dichloromethane) or a mixture of solvents (e.g. ethyl-acetate - acetone) does not result in the required polymorph 1 form, even if a polymorph 1 form of seeding crystal is used, because the polarity of the mixture does not change during the process.

Summary of inventive features

In summary, in order to achieve the goal of the present process – namely, to prepare the product of the less stable polymorph form 1 – one needs all three of the following elements:

1. *In situ* formation of the clopidogrel hydrogensulphate;
2. The presence of seeding crystals of polymorph form 1;
3. Change of solvent polarity during or immediately after reaction of clopidogrel base and sulphuric acid.

Although each of the listed technical features may be known in general in the art, the failures of the experiments in which one feature alone or a combination of two features were used - as a modification of the Lifshitz-Liron technology - dissuade the person of ordinary skill in the art from their use, and especially from the combinations thereof. Accordingly, the present invention is not obvious from the Lifshitz-Liron disclosure.

Objection to specification

On pages 6-7 of the Office Action, objection was raised to the specification. Applicants have amended the specification – without introducing new matter – in order to more idiomatically disclose their invention. The Examiner objects to citations of foreign patent

documents in the specification as allegedly constituting improper incorporation by reference. It is respectfully submitted that the foreign patent documents in question are cited in connection with descriptions of relevant prior art, and that they are not relied upon for disclosure of subject matter essential to the description of the manner of making and using Applicants' invention.

Contact information

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Richard Gallagher (Reg. No. 28,781) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.14; particularly, extension of time fees.

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Respectfully submitted,

By 

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CRYSTALLIZATION TECHNOLOGY HANDBOOK

Second Edition
Revised and Expanded

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. Strathdee, Control of crystal mean
allizer, *I.Chem.E. Trans.*, *75A*, 183-

ntrol of fines suspension density in
CI crystallizer using transmittance
Chem. Eng., *78(4)*, 663–673 (2000).
Wood, Modeling and control of a
, part 2: Model predictive control,
(1999).
Tits, and J. L. Zhou, Avoiding the
nonotone line search II. Inequality
ation. *SIAM J. Num. Anal.*, *29*(4),

combining feasibility, descent and
quality constrained optimization.
3).
's Guide for FSQP Version 3.0b*,
ient, University of Maryland,

inear model predictive control of a
Particle Sci. Tech. J. (in press).
line determination of supersatura-
on based on density measurement,
)4).
trathdee, On-line control of super-
; KCl crystallizer, *Can. J. Chem.*

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Reaction Crystallization

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1. INTRODUCTION

Reaction crystallization, also called precipitation, is an area for which crystallization as well as reaction engineering aspects are important. Classically, crystals are obtained from a solution by (a) cooling, (b) increasing the concentration of the solute through solvent evaporation, (c) combining these two processes when the solvent evaporation is used both for cooling and for concentrating, or (d) by salting or drowning-out with the help of a cosolvent.

Precipitation differs from these classicial processes in that the supersaturation, which is required for the crystallization, no longer results from an action on the physical properties of the solution. It is obtained by a chemical reaction between two soluble components leading to a less soluble product which crystallizes. The reactants can be molecules or ions. The reaction crystallization may proceed via a third intermediate, a dissolved molecule, which becomes solid afterwards. Alternatively, the reactants can directly lead to a very sparingly soluble precipitate. The generated solids can be

crystalline or amorphous. Reticulation of the suspended, solid particles may take place, and the suspension is then called a gel.

In both cases, the reaction and the crystallization occur simultaneously and have their own kinetics. Both have to be taken into account. Thus, it will be necessary to consider the crystallizer as a chemical reactor with complex kinetics and to apply the chemical reaction engineering methodology for its design and characterization. Reaction and crystallization kinetics have to be measured in ideal laboratory reactors. In addition, mixing effects have to be considered in two ways: (a) the global or partial homogeneity of the vessel (also called macromixing), which is a general problem also for classical crystallizers, and (b) the local mixing effects (also called micromixing), particularly near the feed point of the reactants. At this point, in the case of fast reaction kinetics, the supersaturation may be very high and thus high nucleation rates can be observed. Then, reaction and crystallization kinetic rates are faster or in the same order of magnitude than the mixing processes rates, resulting in a competition among mixing, reaction, and nucleation. The mixing kinetics will have a high effect on the yielded crystals, especially on the number concentration of crystals formed and on their size.

Hence, the study of reaction crystallization is more difficult than that of classical crystallization, because the crystal generation depends on several processes, which all have their own kinetics (e.g., chemical reaction, crystallization, and mixing). The competition between these three steps generally results in (a) rapid crystallization and especially nucleation, which is very problematic to keep under control, and (b) multiple zones in the apparatus showing different mixing conditions and, consequently, very different crystallization and reaction conditions. Therefore, it is necessary to split the reactor into ideal zones, each zone having given mixing parameters, global reaction crystallization kinetics, and subsequent mechanisms influenced by mixing. As an example, in a stirred, single-jet, semibatch vessel, one can distinguish the input zone and the agitator zone, which have very different mixing and concentrations levels than those of the remainder of the reactor. These considerations are a classical approach used in chemical reaction engineering. This approach has, for instance, successfully been applied to fast chemical kinetics, leading to a solute which crystallizes afterward (salicylic acid precipitation by chemical reaction between sodium salicylate and sulfuric acid [1.1]), and to the direct precipitation of a sparingly soluble salt after a chemical reaction (sodium perborate crystallization [1.2]). To obtain a rational optimal approach of the development of precipitation processes, it seems to be necessary to go on in this direction and to improve this methodology, which is described in detail in the following pages.

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Due to the complexity of the reaction crystallization, the following steps are to be studied:

1. The kinetics of the chemical reaction leading to the supersaturation. These kinetics are often very fast, especially when combining ionic species or for acid–base reactions, leading, in turn, to high local supersaturation. In some cases, these kinetics can be complex, for gas–liquid reactions or for organic reactions between molecules, for example.
2. The kinetics of crystallization, including primary and secondary nucleation, growth, agglomeration and Ostwald ripening, which can be considered as important mechanisms during the precipitation of very small particles. The species are often ionic components and, as an example, growth can be considered as a rather complicated step, because one has to take into account the surface integration and the diffusion of two ions. Chiang and Donohue have proposed pertinent models for the growth of crystals from ionic solutions [1.3].
3. The kinetics of mixing, which can have a high effect on both reaction and crystallization kinetic rates if they are of the same order of magnitude. Both macromixing and micromixing have to be considered in this case.

A modeling of the precipitator needs to consider all of these phenomena and their interactions. It is especially important to take into account the mixing models if crystallization and/or reaction kinetics is fast. Then, the vesesel can no longer be considered as a perfect mixed reactor.

2. DRIVING FORCE OF REACTION CRYSTALLIZATION

2.1. Solubility

Two possibilities are to be considered, and we will find this duality in all our discussions:

1. The chemical reaction leads to a more or less soluble molecule P, which then crystallizes. This is the case for many compounds (e.g., salicyclic acid precipitation from sodium salicylate and sulfuric acid).

   $$A + B \rightleftharpoons P \rightleftharpoons S\,(\text{solid})$$

   The first reaction can either be at equilibrium or with finite rates in both directions. For such problems, the solubility of component P can be described as the molar concentration of P in the solution at the thermodynamic solid–liquid equilibrium. This concentration is a function of temperature (see Chapters 1 and 8).

2. The chemical reaction does not lead to any intermediate soluble species and the solid crystallizes directly from the reactants. This is the case of many ionic reactions, leading to a sparingly soluble salt, between a cation and an anion.

$$xA^{z+} + yB^{z'-} \leftrightarrow A_xB_y \text{ (solid)}$$

with the electroneutrality condition

$$xz = yz'$$

In case 2, the thermodynamic equilibrium will be described by the solubility product, which is a function of temperature, and is defined by

$$k_a = a_{Ae}^x a_{Be}^y \tag{2.1}$$

where a_{Ae} is the activity of the cation A^{z+} and a_{Be} is the activity of the anion $B^{z'-}$ at equilibrium, given by

$$a_{Ae} = f_z[A^{z+}]_e \tag{2.2a}$$

$$a_{Be} = f_{z'}[B^{z'-}]_e \tag{2.2b}$$

$[A^{z+}]_e$ and $[B^{z'-}]_e$ are the molar concentrations of the two ions at equilibrium conditions. f_z and $f_{z'}$ are the activity coefficients of ions A^{z+} and $B^{z'-}$. The solubility of the electrolyte A_xB_y can be expressed by a concentration C^* at thermodynamic equilibrium, calculated from

$$C^* = \frac{[A^{z+}]_e}{x} = \frac{[B^{z'-}]_e}{y} \tag{2.3}$$

The representation of this concentration as a function of temperature is the solubility curve and generally solubility increases with temperature (see Fig. 2.1). The use of the mean ionic activity $a_\pm$ is defined with respect to mean ionic concentration C (C^* at equilibrium) and the mean ionic activity coefficient $f_\pm$ by

$$a_\pm = (x^x y^y)^{1/(x+y)} C f_\pm \tag{2.4}$$

with

$$f_\pm = (f_z^x f_{z'}^y)^{1/(x+y)}$$

The activity coefficients f_z and $f_{z'}$ can be calculated with help of very sophisticated models [2.1] in the general case. For dilute solutions, a rather good precision can be obtained from the well-known Debye and Hückel equation

$$\log_{10}(f_\pm) = -A_{DH} z z' I^{0.5} \tag{2.5}$$

where I is the ionic force of the solution (mol/L) given by

$$I = \frac{1}{2}\sum_i C_i z_i^2 \tag{2.6}$$

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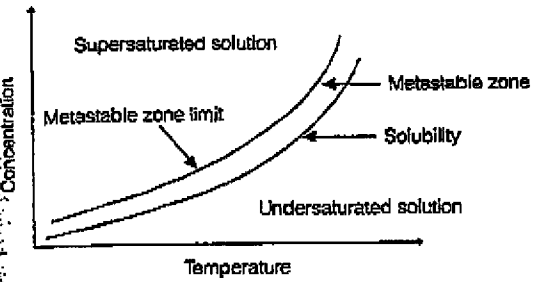

Figure 2.1. Solubility and metastable zone.

C_i is the concentration of ion i and z_i is its valency.
A_{DH} is a constant for a given temperature: 0.5 at 15°C, 0.509 at 25°C, and 0.553 at 65°C (see Appendix A1). In many cases and particularly for $C_i \leq 0.02$ mol/L, the application of this very simple law allows one to obtain a precise enough value of $f_\pm$. For other cases, one will find useful information in Ref. [2.2]. The solubility product becomes

$$K_a = f_z^x f_{z'}^y [A^{z+}]_e^x [B^{z'-}]_e^y = f_\pm^{x+y} [A^{z+}]_e^x [B^{z'-}]_e^y \tag{2.7}$$

enables one to calculate the concentration product at equilibrium

$$K_e = \frac{K_a}{f_z^x f_{z'}^y}$$

and the equilibrium concentration C^*

$$C^* = \left(\frac{K_e}{x^x y^y}\right)^{1/(x+y)} \tag{2.8}$$

ery sparingly soluble salts, solubility concentrations are very low and comes close to 1. In this case, $K_a = K_e$.
last, Ostwald and Freundlich have shown that solubility depends on particle size: It increases if the particle size decreases. The obtained effect is important only for very small particles, as the one crystallized in a precipitation process. For particles that are supposed to be spherical with diameter L, solubility may be written

$$C(L) = C^*(L \to \infty) \exp\left(\frac{4\bar{M}_S \gamma_{CL}}{\nu \rho_C \Re T L}\right) \tag{2.9}$$

variations resulting from equation (2.9) are only perceptible for very small (< 1 μm). The consequences of this phenomenon are generally